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Previews

This Little pIgR Went to the Mucosa

In this issue, Hamburger et al. (2004) report the structure of the terminal domain of the polymeric immunoglobulin receptor (pIgR), which mediates the "suicide" transcytosis of multimeric immunoglobulins (IgA, IgM). This assists in reconciling decades of biochemistry, revealing a long-puzzling interaction.

Two of the five human antibody isotypes (IgA, IgD, IgE, IgG, and IgM) can multimerize, through intermolecular disulfide bonds, forming dimers to tetramers (IgA) or pentamers and hexamers (IgM). The cystine linkages are either directly between short C-terminal extensions of the heavy chains ("tailpieces") or to a small accessory molecule, "joining" or J chain (Johansen et al., 2001). The importance of the multimeric immunoglobulins, particularly IgA, is that they are the preponderate antibodies found in the mucosa: the linings of the eye and the genital, respiratory, and gastrointestinal tracts. Since these surfaces represent the predominant routes of entry for a variety of pathogens, components of humoral immunity that function here have long been appreciated as the "first line of defense" of the immune system. Indeed, the amount of IgA secreted into the intestinal lumen alone exceeds the total amount of IgG produced in the body on a daily basis.

While the mucosal epithelium serves as an impermeable barrier, walling these compartments off from the rest of the organism, it also functions to segregate immune effector cells from invading organisms in the lumen. To straddle this barrier, the immune system utilizes specialized cellular structures (M cells, Peyer's patches) and active transport pathways (transcytosis). To export multimeric antibodies secreted by plasma cells (end-stage differentiated B cells, comprising part of the lymphoid tissue associated with mucosal epithelium), a receptor specific for multimeric antibodies, the polymeric immunoglobulin receptor (pIgR), is expressed on epithelial cells, initially targeted to basolateral surfaces (Mostov, 1994). Here, pIgR noncovalently interacts with ligand and is endocytosed. During or after transcytosis to the apical surface of the cell, disulfide-exchange occurs between pIgR and IgA, covalently coupling the complex, and the pIgR extracellular moiety is hydrolytically cleaved, releasing the complex into the extracellular space—hence the characterization of the transport as "suicidal". The solubilized extracellular fragment of the pIgR is termed secretory component (SC); the complex is termed secretory IgA (sIgA). Transcytosis of pIgR also occurs constitutively, resulting in the secretion of free SC. Targeting is mediated by separable sequence elements located in the pIgR cytoplasmic domain; pIgR has long served as a model system for studying directed transcytosis in polarized cells (Mostov and Cardone, 1995).

SC likely serves several functions beyond providing covalent and noncovalent interactions with polymeric antibody ligands (Phalipon and Corthésy, 2003). It has long been proposed that SC protects IgA from proteolytic degradation in the relatively inhospitable environment of the mucosa. Emerging evidence also suggests that free SC may also act directly to prevent pneumococcal infections independently of antibody-mediated mechanisms, by blocking adherence, or may even be coopted by some invading bacteria to infect epithelial cells by accessing the transcytotic machinery.

While the pIgR ectodomain was almost immediately recognized as consisting of a tandem repeat of five Ig V-like domains, it remained for the crystallographic analysis of the N-terminal, Ig binding domain, D1, (Hamburger et al., 2004) to reveal the unique aspects of this example of the superfamily—having to overcome, in the process, an infrequent, but not unprecedented, type of twinning associated with special cases of monoclinic space groups. In particular, the pIgR D1 CDRs display highly noncanonical conformations: a turn of helix in CDR1, a very short, tightly-turning CDR2 and a distinct, tilted CDR3 conformation. These features not only have implications for the nature of the Ig binding site but also limit possible intermolecular associations. As would be expected, residues identified through years of previous peptide binding and directed mutagenesis studies as affecting affinity are exposed as exerting these effects both directly, by providing ligand contacts, and indirectly, by affecting local conformation. However, identifying which is which is only now possible in light of the three-dimensional structure. These studies also extend, and beautifully complement, previous results from this group detailing how antibodies (IgG, in this case) are imported across the epithelium by the FcRn (Raghavan and Bjorkman, 1996) and by structural analyses of part of one pIgR ligand, Fcα (Herr et al., 2003).

The complementary surface plasmon resonance binding experiments performed by Hamburger and coworkers (2004) show consistently, but most definitively, that pIgR has significant affinity only for multimeric antibody species that include J chain and that neither inclusion of tailpieces alone, nor the glycosylation state of the pIgR D1, affect binding. The parsimonious, though by no means conclusive, explanation to account for the data is that J chain forms part of the footprint of pIgR. The structure of J chain (which has no recognizable sequence similarity to any protein of known structure) and its role in polymeric immunoglobulin assembly and pIgR binding, are now the leading mysteries of this story.

Given the range of interactions observed in previously studied Ig/receptor complexes, and the complexity of dimeric IgA (two IgAs with tailpieces plus J chain), the topological possibilities for the complete sIgA complex are myriad. It has been argued, on the basis of the Fcα/FcαRI complex structure (Herr et al., 2003), that the footprints of FcαRI and pIgR on dimeric IgA likely overlap, but the detailed interactions are very likely dissimilar, paralleling the distinct structures of pIgR and FcαRI. The extant binding data seem to preclude an IgE/

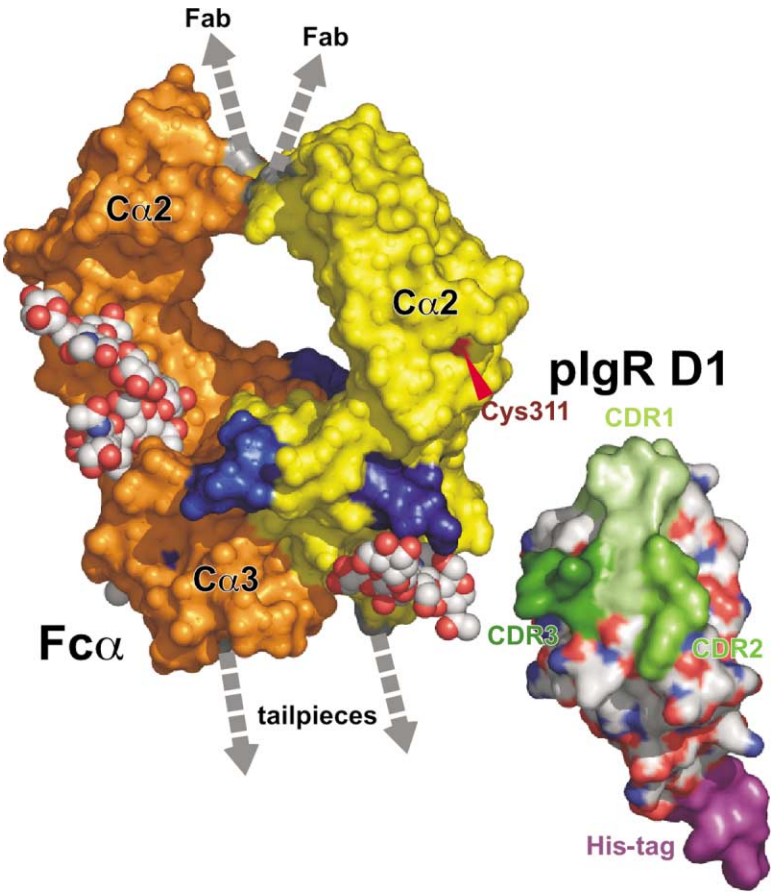

Figure 1. Interaction Surface Maps of Fcα and pIgR D1

Molecular surface representations of Fcα (Herr et al., 2003) and pIgR D1 (Hamburger et al., 2004) domains are shown, colored by chain (yellow or orange) for Fcα and by atom type (carbon, gray; oxygen, red; nitrogen, blue) for pIgR. Ordered carbohydrates in the Fcα structure are shown as spheres, also colored by atom type. Putative interaction surfaces are indicated: residues 402–410 (blue), residues 430–443 (dark blue), and cysteine 311 (red) on the IgA Fc and the pIgR CDRs (shades of green). The oblique view of the Fc is necessitated by the somewhat buried location of cysteine 311. What is not shown are the IgA Fabs, tailpieces, J chain or the whole other IgA molecule in the dimer, or the remaining four Ig domains of SC. The figure was prepared with PyMOL (DeLano, W.L. *The PyMOL Molecular Graphics System* [2002]; http://www.pymol.org).

FcεRIα-type interaction (Garman et al., 2000), with significant SC/Cα2 interactions, but the numerous points of flexibility in all these molecules leave many possibilities open. The complexity, and potential multivalency, of the ligand is sufficient that even discontinuous surfaces on opposite sides of the pIgR D1 domain, as suggested by some of the mutagenesis studies, might make bridging interactions. It even remains formally possible, though admittedly unlikely, that pIgR threads its way through the large aperture in Fcα (Figure 1).

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Selected Reading

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